

## REMARKS / ARGUMENTS

### 1. Telephonic Interview with Examiner Gross on September 30, 2010

The Applicants thank Examiner Gross for granting a telephonic Interview with the Applicants and Applicants' representatives on September 30, 2010. A Communication to Record Substance of Interview is submitted concurrently with the present Response.

### 2. Claim status and amendment to claims

Claims 40 and 45-53 are pending in the present application.

Claim 40 has been amended to correct a typographical error in the spelling of the word "an." It has also been amended for clarity by amending the punctuation and by reciting "an organic functional group wherein the organic functional group comprises a mercapto substituent." It has also been amended, as suggested by the Examiner, to recite that the organic fluorescent compound is throughout the silica-based core.

Claim 47 has been amended to recite that the ligand is conjugated to the nanoparticle by a linkage, wherein the linkage is an ester, an amide, a thioester or a sulfate ester linkage.

Support for the amendments to claims 40 and 47 may be found throughout the original specification and claims as discussed below.

Claim 45 has been amended to recite the additional ligands "biopolymer" and "synthetic polymer." Support for the amendment of claim 45 is found at paragraph 0047 of U.S. Patent Application Ser. No. 10/306,614 filed Nov. 26, 2002 ("the '614 application," US2004/0101822), the disclosure of which is incorporated by reference in the present application.

New claim 54 has been added. Support for new claim 54 is found at paragraph 0039 of the '614 application (US2004/0101822).

No new subject matter has been introduced.

### 3. Replacement Form SB08 filed concurrently

The Examiner has objected to the Information Disclosure Statement filed on February 28, 2006 because citation nos. A-F and H on Form SB08b do not include the

journal name plus volume (publisher) or the publication date. In response, the Applicants submit Replacement Form SB08 listing complete bibliographic information for citation nos. A-F and H.

The Applicants respectfully request that the Replacement Form SB08 be substituted for the Form SB08 previously filed on February 28, 2006.

4. Claim rejection under 35 U.S.C. § 103(a) should be withdrawn because the claims are non-obvious over the cited references.

Claims 40 and 45-53 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Battersby et al. ("Battersby," WO 00/32542) in view of Ichinose et al. ("Ichinose," 1993 Chemistry Letters p 1961-1964). The Applicants respectfully traverse the rejection.

At page 7 of the Office Action, the Examiner states that "absent evidence to the contrary, the PTO has sound basis for believing that the microspheres of Battersby et al appear identical and/or are produced by a substantially identical process." Furthermore, the Examiner states that "[o]ne of ordinary skill in the art would have been motivated to derivatize the seed silica cores of Battersby et al with MPS for reaction with a maleimide according to Ichinose et al."

The Applicants respectfully submit that the proposed combination of Battersby and Ichinose is not sufficient to create prima facie obviousness for the following reasons.

At page 5 of the Office Action, the Examiner states that Example 3 of Battersby (page 39, line 19 to page 40, line 4) teaches fluorescently-labeled silica microspheres for encoded solid-phase synthesis, specifically, that 2-3 nm and smaller silica seed crystals can be derivatized with aminopropylsilane (APS) followed by fluorescein isothiocyanate (FITC) using the method of van Blaaderen et al. ("van Blaaderen," Ref. D of record, 1992, Synthesis and Characterization of Colloidal Dispersions of Fluorescent, Monodisperse Silica Spheres Langmuir 8: 2921-2931) to make labeled silica microspheres. The Applicants respectfully disagree that the teachings of Battersby, in combination with Ichinose, render the presently pending claims obvious.

At page 39, line 28 - page 40, line 2, Battersby discloses that sols of 10 to 130 nm in diameter can be prepared by raising the pH of dilute sodium silicate solution and that smaller particles ( $< 3\text{nm}$ ) can be dissolved and deposited on the larger particles at a uniform rate via Ostwald ripening. The particles formed have cores consisting of pure silica. Battersby does not teach, alone or in combination with Ichinose, particles having a silica-based core comprising an organic functional group wherein the organic functional group comprises a mercapto substituent; and an organic fluorescent compound throughout the silica-based core.

Following the teachings of Battersby and using the method of van Blaaderen taught therein, one of ordinary skill in the art would not expect to succeed in forming a fluorescent silica-based nanoparticle wherein an organic fluorescent compound is present throughout the silica-based core. Moreover, while the Applicants agree that the stable sols of 10-130 nm taught by Battersby can overlap with the ranges of core radii claimed in pending claims 52 and 53, and with the ranges of nanoparticle diameters claimed in pending claims 40 and 45, the chemical composition and architecture of the claimed core-shell nanoparticle (i.e., fluorescent silica-based nanoparticle comprising (a) a silica-based core comprising an organic functional group wherein the organic functional group comprises a mercapto substituent, and an organic fluorescent compound throughout the silica-based core; and (b) a silica shell surrounding at least a portion of the core) is fundamentally different from the one suggested by the Examiner (see page 5 line, last line, to page 6, line 3 of the Office Action) and is not taught or suggested by Battersby.

Paragraph [0042] of the present specification discloses that the silica-based core of the claimed nanoparticle may be synthesized by using a co-reactive organosilane, which method one of skill in the art would recognize as producing organosilane throughout the silica-based core, in contrast to the teachings of Battersby and Ichinose.

The specification discloses one exemplary process for manufacturing fluorescent core-shell nanoparticles in which the core comprises an organic functional group comprising a mercapto substituent group and an organic fluorescent compound positioned within or throughout the silica-based core.

By contrast, in the core-shell architecture proposed by the Examiner, the core of the particle is pure silica. Derivatizing this pure silica core with APS and FITC as a shell layer according to the method of van Blaaderen, and subsequently growing a pure silica shell covering 100% of the core surface area, would not produce the nanoparticle claimed in claim 40 (and in claims 45-53 depending therefrom) that has an organic fluorescent compound throughout the silica-based core.

Exhibit 1 is a schematic drawing that shows these differences between the architecture of (A) the nanoparticle claimed in claim 40 (and claims 45-53 depending therefrom), which has an organosilane present throughout the core (i.e., a silica-based core comprising an organic functional group comprising a mercapto substituent), and (B) the nanoparticle proposed by the Examiner, which has a core of pure silica.

The Applicants therefore submit that since Battersby does not teach a silica-based core comprising an organic functional group comprising a mercapto substituent, and since the van Blaaderen method taught by Battersby to produce nanoparticles is not suitable for producing the nanoparticles of claim 40 (and claims 45-53 depending therefrom) Battersby does not render obvious the presently claimed nanoparticles. Furthermore, the proposed combination of Battersby with Ichinose does not cure this defect.

In view of the above arguments, the Applicants respectfully request that the rejection of claims 40 and 45-53 under 35 U.S.C. § 103(a) be withdrawn.

5. Claim rejection under 35 U.S.C. § 112 should be withdrawn because claims are supported by specification as filed.

Claims 46 and 47 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the specification as originally filed provided no implicit or explicit support for ligands including proteins, peptides or oligopeptides, as set forth in new claim 46 or linkages including esters, thio[esters, amides or sulfate esters, as set forth in claim 47. The Applicants respectfully traverse the rejection.

**Support for claim 46.** Paragraph [0001] of the published application (US20060183246) indicates that the application is a continuation-in-part based on non-

provisional application U.S. Ser. No. 10/306,614 (“the ‘614 application”) filed Nov. 26, 2002, the disclosure of which is incorporated by reference. The Applicants submit that claim 46 is fully supported by the disclosure of the ‘614 application.

Paragraph [0090] of the ‘614 application (US20040101822) states that “[t]herapeutic agents that can be incorporated with the fluorescent nanoparticles or the ligated-fluorescent nanoparticles of the invention include nucleosides, nucleoside analogs, oligopeptides, polypeptides . . . .”

Paragraph [0129] of the ‘614 application (US20040101822) states that “[t]he silica shell surface of the nanoparticles can be further modified if desired by, for example, surface functionalization reactions using known cross-linking agents to afford surface functional groups and as illustrated herein. Crosslinking agents are, for example, divinyl benzene, ethylene glycol dimethacrylate, trimethylol propane trimethacrylate, N,N'-methylene-bis-acrylamide, alkyl ethers, sugars, peptides, DNA fragments, or other known functionally equivalent agents.”

Paragraph [0151] of the ‘614 application (US20040101822) states that “[t]he surface of the nanoparticles can be further chemically modified to improve the versatility and stability of the nanoparticles, for example, introducing carboxylic acid groups or like chemical functional groups. Introducing functional groups, such as carboxylic acid groups, to the surface of silica coated nanoparticles can provide attachment points to enable covalent attachment of bio-molecules, for example, proteins and antibodies, to the surface of the nanoparticles.”

Thus the Applicants submit that the specification supports the limitation of claim 46 “wherein the ligand comprises at least one of a protein, a peptide, or an oligopeptide.”

**Support for claim 47.** Claim 47, as presently amended, recites “[a] fluorescent silica-based nanoparticle of claim 40, wherein the ligand is conjugated to the nanoparticle by a linkage, wherein the linkage is an ester, an amide, a thioester or a sulfate ester linkage.”

In support of this amendment, the Applicants note that paragraph [0126] of the ‘614 application discloses that “[d]epending on the reactive functional group (X.sub.1 or

X.sub.2) of the ligand, a corresponding functional group (Z.sub.1 or Z.sub.2) can be selected from the following table, to provide an ester linkage, thioester linkage, or amide linkage in the ligated-fluorescent nanoparticle or linked product.

Table 1 that follows paragraph [0126] discloses that the resulting linkage in the ligated-fluorescent nanoparticle can be an ester, an amide, a thioester or a sulfate ester.”

Thus the Applicants submit that the ‘614 specification supports amended claim 47.

In view of the above arguments, the Applicants respectfully request that the rejection of claims 46 and 47 under 35 U.S.C. § 112, first paragraph, be withdrawn.

6. Claim rejection under 35 U.S.C. § 112 should be withdrawn because claims have been amended to cure indefiniteness.

At page 10, claim 40 and claims 45-53 depending therefrom, are rejected under 35 U.S.C. § 112, second paragraph, as failing to comply with the written description requirement. The Examiner states that claim 40 recites vague and indefinite language.

As discussed above in Section 2, claim 40 has been amended to correct a typographical error in the spelling of “an,” thus rendering the claim definite and drawn to a fluorescent silica-based nanoparticle comprising (a) a silica-based core comprising an (i.e., one) organic functional group wherein the organic functional group comprises a mercapto substituent. Claim 40 has also been amended for clarity by amending the punctuation. It has also been amended, as suggested by the Examiner, to recite that the organic fluorescent compound is throughout the silica-based core.

**CONCLUSION**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 50-0289 referencing Docket No. 1258\_3378US.

Respectfully submitted,

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